REMARKS

Claims 19, 21-28, 63-78, 90, 92-103, 105-114, and 117-149 were pending in the present application. Claims 122-125 and 135-149 were withdrawn by the Examiner. Applicant has canceled claims 117-126 and 129-146, without prejudice. Claims 25, 65, and 96 have been amended to clarify that which Applicants regard as the invention. Specifically, claims 25, 65, and 96 have been amended to recite that the immunostimulatory oligonucleotide comprises at least one chemical group selected from the group consisting of phosphorothioate, alkylphosphonate, phophorodithioate, alkylphosphorothioate, phosphoramidate, 2-O-methyl, carbamate, acetamidate, carboxymethyl ester, carbonate, and phosphate triester. Support for this amendment can be found in the specification, for example, at page 9, line 14 to page 10, line 9.

Claims 64, 67, 68, 70, 72, 74, 76, and 90 have been amended to improve readability of the claims. Specifically, claims 64, 67, 68, 70, 72, 74, 76, and 90 have been amended to recite (1) administering an amount of the immune adjuvant composition as claimed to the individual; and (2) administering a nucleic acid molecule comprising a nucleotide sequence encoding the antigen to the individual. Moreover, the phrase "wherein the nucleic acid molecule is administered separately from the immune adjuvant composition or in the same formulation with the immune adjuvant composition" has been deleted as unnecessary since it is clear that such is the case.

No new matter has been added by these amendments. Upon entry of this amendment, claims 19, 21-28, 63-78, 90, 92-103, 105-114, and 127-128 will be pending in the present application.

Applicant respectfully requests that the amendments and remarks made herein be entered and fully considered.

I. Claim Objections

The Examiner alleges that the term "groups" in claims 25, 65, 66, 96, 97 and 110 should be "group." Applicant respectfully disagrees. However, Applicant has amended claims 25, 65, and 96 to recite "at least one group." Claim 66 is dependent upon claim 65. Claims 97 and 110 do not recite the term "groups," nor are they dependent upon a claim reciting the term "groups." Thus, the claim objection has been rendered moot.

The Examiner contends that claims 64, 67, 68, 70, 72, 74, 76, and 90 should specify (1) administering an amount of the immune adjuvant composition as claimed to the individual; and (2) administering a nucleic acid molecule comprising a nucleotide sequence

encoding the antigen to the individual. The Examiner also contends that the phrase "wherein the nucleic acid molecule is administered separately from the immune adjuvant composition or in the same formulation with the immune adjuvant composition" is not needed. Applicants have amended the claims accordingly. As the phrase "in the same composition" in claims 64, 67, 68, 70, 72, 74, 76, and 90 has been deleted, the Examiner's suggestion to add the term "together" has been rendered moot.

The Examiner contends that, in claim 120, the phrase "is selected from the group comprising" should be "selected from the group consisting of" to be in proper Markush format. Claim 120 has been canceled. Thus, the rejection has been rendered moot.

The Examiner contends that, in claims 121, 126, 131, and 134, the Markush group is not in proper format because the word "or" is used. Claims 121, 126, 131, and 134 have been canceled. Thus, the rejection has been rendered moot.

The Examiner contends that claims 121, 126, and 134 are unclear because (1) a "solution" is equivalent to a "suspension" and "elixir"; (2) a "liquid solution" is redundant; (3) a "sterile liquid or solution" is a species within the species of "liquid or solution"; (4) a suspension or elixir for oral administration" is a species within the species of "liquid or solution"; and (5) the species within the Markush group use the word "or." Claims 121, 126, and 134 have been canceled. Thus, the rejection has been rendered moot.

The Examiner contends that claim 133 is not in proper Markush format because it does not have an "and" separating the species and uses the term "comprising." Claim 133 has been canceled. Thus, the rejection has been rendered moot.

II. Rejections Under 35 U.S.C. § 112

A. The Rejections Under 35 U.S.C. § 112, first paragraph

Claims 64, 67, 68, 70, 72, 74, 76, 90, 92-103, 105-114, 127 and 128 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

Specifically, claims 64, 67, 68, 70, 72, 74, 76, 90, 103, and 127 were rejected as containing new matter because the specification allegedly does not support administering 1) a saponin and an immunostimulatory oligonucleotide; and 2) a nucleic acid encoding an antigen. Specifically, the Examiner contends that "it is not readily apparent that applicants contemplated administering a nucleic acid sequence encoding an antigen because the

antigen in the paragraph bridging pg 14-15 refers to the antigen 'suitable for the enhanced immune response' and is not limited [to] the antigen used in the composition on pg 16, lines 12-15, or page 18, lines 9-11." Moreover, the Examiner contends that it is not "readily apparent that applicants contemplated administering a nucleic acid sequence encoding an antigen together with or separately from administering a saponin and immunostimulatory oligonucleotide." Applicant respectfully disagrees.

The Examiner alleges that page 10, lines 10-12 of the specification does not refer to the combination of QS-7, QS-17 or QS-18 with an oligonucleotide with at least one unmethylated CpG dinucleotide as required by claim 64. While support for this combination may not be present at the specific location cited by the Examiner, the combination of QS-7, QS-17, QS-18 or QS-21 with an oligonucleotide with at least one unmethylated CpG dinucleotide is fully supported by the specification. The specification describes an immune adjuvant composition comprising a saponin adjuvant and an immunostimulatory oligonucleotide. See the specification at page 11, lines 1-2. The saponin may be QS-7, QS-17, QS-18 or QS-21. See the specification at page 11, lines 5-9. The immunostimulatory oligonucleotide preferably comprises at least one unmethylated CpG dinucleotide. See the specification at page 11, lines 17-18.

The Examiner contends that it is not readily apparent that Applicant contemplated administering a nucleic acid sequence encoding an antigen. Firstly, the specification explicitly conveys that the term "antigen" as used in the specification includes, *inter alia*, a nucleic acid sequence encoding an antigen. The paragraph bridging pages 14 and 15 explicitly states that the antigen may be a protein, a peptide, a polysaccharide, a lipid, a glycolipid, a phospholipid, or a *nucleic acid encoding the antigenic protein or peptide of interest*. The paragraph immediately following states "Accordingly, in a third aspect, the invention also encompasses a vaccine composition comprising a saponin adjuvant, an immunostimulatory oligonucleotide, and an antigen." The use of the term "accordingly" connects the concepts in these two paragraphs and makes it clear that (i) the specification explicitly contemplates the use of a nucleic acid encoding an antigen, and the use of compositions comprising such a nucleic acid, a saponin adjuvant, and immunostimulatory oligonucleotides; and (ii) throughout the specification, the term "antigen" is used, *inter alia*, to mean a nucleic acid encoding an antigenic protein or peptide of interest[1]. Moreover,

[1] It would be clear to the skilled artisan that such was done for purposes of efficiency in describing the invention, in order to render it unnecessary to repeat "a protein, a peptide, a polysaccharide, a lipid, a

claims 18 and 62 of the specification as originally filed provide for compositions and methods for increasing the immune response wherein the antigen comprises "a protein, a peptide, a polysaccharide, a lipid, a glycolipid, a phospholipid, or *a nucleic acid encoding the protein or peptide*" (emphasis added). The claims as filed are deemed part of the original disclosure. *In re Benno*, 768 F.2d 1340 (Fed. Cir. 1985).

Secondly, Applicant respectfully points out that the Examiner is misapplying the standards of the written description requirement of section 112. As noted in Applicant's Amendment of April 26, 2004, "a disclosure need only reasonably convey to persons skilled in the art that the inventor had possession of the subject matter in question." *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 USPQ 2d 1895, 1904 (Fed. Cir. 1996). It is a well-established principle of patent law that an applicant is entitled to be his or her own lexicographer. *Hormone Research Foundation Inc. v. Genentech Inc.*, 904 F.2d 1558, 1563 (Fed. Cir. 1990). In the paragraph bridging pages 14 and 15, Applicant clearly defines an antigen as including a protein, a peptide, a polysaccharide, a lipid, a glycolipid, a phospholipid, or a nucleic acid encoding the antigenic protein or peptide of interest. Thus, absent a contrary definition, this meaning should be applied throughout the specification. Accordingly, it is clear that the specification conveys the definition of antigen as including a nucleic acid encoding an antigen.

Claim 113 stands rejected and new claim 127 was rejected because the phrase "wherein the nucleic acid encoding the antigen is administered to the individual or test system within 0-2 days of the administration of the immune adjuvant composition" allegedly remains new matter. The Examiner alleges that the specification does not contemplate administering a nucleic acid sequence encoding an antigen and a mixture of saponin and immunostimulatory oligonucleotide. Moreover, the Examiner alleges that one of skill cannot extrapolate administering A and B+C separately.

Applicant respectfully disagrees. For the reasons discussed above, the specification clearly contemplates administering a nucleic acid sequence encoding an antigen and a mixture of saponin and immunostimulatory oligonucleotide.

Applicant reiterates her position that there are only four possibilities when saponin (A), oligonucleotide (B) and antigen (C) are administered separately, since separate administration would reasonably convey to the person of skill in the art that the order of

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glycolipid, a phospholipid, or a nucleic acid encoding the antigenic protein or peptide of interest" everywhere that "antigen" is used in the specification.

administration can differ. Thus, the four possibilities for separate administration are: (1) administer saponin, oligonucleotide, and antigen separately (A+B+C; A+C+B; B+A+C; B+C+A; C+A+B; and C+B+A); (2) administer saponin and oligonucleotide together, antigen separately (AB+C; C+AB); (3) administer saponin and antigen together, oligonucleotide separately (AC+B; B+AC); and (4) administer oligonucleotide and antigen together, saponin separately (BC+A; A+BC). This is an extremely small genus, and, in the case of a limited genus, each member is adequately described without specifically naming each species.

In the Office Action mailed August 11, 2004, the Examiner has come up with 13 species within the genus by introducing a time variable: the order in time of the administration of each component. While Applicants do not agree that this was proper, the 13 different combinations of the Examiner are still less that the class of 20 compounds described in In re Petering (301 F.2d 676, 682 (C.C.P.A. 1962) (holding each compound within a class of 20 compounds adequately described by a generic structure)). Moreover, since the specification repeatedly teaches saponin and CpG oligonucleotide together in a composition, for example, on page 11, lines 1-2, a person of ordinary skill in the art would understand that the specification contemplates administration of saponin and oligonucleotide together, and antigen separately.

For the above reasons, Applicant respectfully requests withdrawal of the rejections under 35 U.S.C. § 112, first paragraph.

B. The Rejections Under 35 U.S.C. § 112, second paragraph

Claims 121, 126, 131, and 134 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Specifically, the Examiner contends that claims 121, 126, 131, and 134 are indefinite because the phrase "such as" makes it unclear whether the limitations following the phrase are part of the claimed invention. Applicant has canceled claims 121, 126, 131, and 134. Thus, the rejection under 35 U.S.C. § 112, second paragraph has been rendered moot.

III. Rejections Under 35 U.S.C. § 103

Claims 19, 21-27, 63-68, 73-77, 90, 95-98, 100-102, 113, and 114 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Weiner *et al.*, 1997, *PNAS* 94:10833-10837 ("Weiner") in view of Kensil, 1996, *Critical Reviews in Therapeutic Drug Carrier*

Systems 13:1-55 ("Kensil") (Office Action, paragraph III). Claims 19, 21, 24, 25, 27, 28, 65, 67, 69, 70, 73-77, 90, 95-98, 100-102, 113, and 114 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Weiner in view of Kensil (Office Action, paragraph IV). Claims 19, 21-27, 63-68, 71-78, 90, 95-98, 100-102, 113, and 114 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Chu *et al.*, 1997, *Journal of Experimental Medicine* 186:1623-1631 ("Chu") in view of Kensil (Office Action, paragraph V). Applicant respectfully disagrees.

According to the Examiner, Weiner discloses that administration of oligonucleotides 1643 and 1758 increased the humoral immune response in a mouse. The Examiner states that oligonucleotide 1643 has three unmethylated CpG motifs and has a phosphorothioate modified nucleotide, and that oligonucleotide 1758 has unmethylated CpG motifs and is equivalent to SEQ ID NO:1 of the present invention. The Examiner adds that oligonucleotide 1758 has a phosphorothioate modified nucleotide. Weiner does not disclose the combination of such immunostimulatory oligonucleotides and a saponin.

According to the Examiner, Chu teaches administering phosphorothioate oligonucleotide 1826 or 1760 as an adjuvant to increase the IgG2a immune response in a mouse. The Examiner states that phosphorothioate oligonucleotide 1826 or 1760 has unmethylated CpG motifs and 1826 is equivalent to SEQ ID NO:2 of the instant invention. The Examiner admits that there is no suggestion in Chu, however, to combine the phosphorothioate oligonucleotides with QuilA, QS-7, QS-17, QS-18, or QS-21.

According to the Examiner, Kensil teaches the use of the saponin adjuvant QS-7, -17, -18, or -21 in combination with vaccines for an adjuvant effect and with other adjuvants to increase the adjuvant effect. The Examiner contends that it would have been obvious to combine the two known adjuvants (the immunostimulatory oligonucleotide containing unmethylated CpGs of SEQ ID NO: 1 or SEQ ID NO: 2 and QS-7, -17, -18, or -21), particularly in light of a teaching in Weiner that provides an invitation to experiment with combinations of immunostimulatory oligonucleotides with other adjuvants.

As a preliminary matter, the Examiner alleges that provisional application 60/095,913, filed August 10, 1998, did not teach any synergy and, therefore, the effective filing date for administering oligonucleotide 1826 with saponin is April 8, 1999. First, Applicants emphasize that there is no requirement that synergy be taught in the specification in order to rely on synergy to show nonobviousness. See *In re Chu*, 66 F.3d 292, 299 (Fed. Cir. 1995). Second, the results described in Examples 1-3 of provisional application 60/095,913 demonstrate synergy in that significant induction of CTL or IgG2a

was observed with the combination of a CpG oligonucleotide and a suboptimal dose of QS-21. No induction of CTL or IgG2a was observed with a suboptimal dose of QS-21 alone or with a CpG oligonucleotide alone. Synergy was also observed with respect to IgG1 (See FIG. 3).

In response to the rejections, Applicant reiterates her position that the unexpected result of synergism of CpG oligonucleotides and QS saponins has been demonstrated, thereby rebutting any *prima facie* case of obviousness.

The Examiner contends that the unexpected results do not represent the genus of saponin and CpG oligonucleotides because some species within the genus cause expected results. The Examiner appears to be arguing that the species is each individual combination of QS-21 and a CpG oligonucleotide at each individual concentration tested. Applicant respectfully submits that the Examiner's contention is not the applicable standard of patent law. The appropriate species is each CpG oligonucleotide or QS saponin. Each CpG oligonucleotide tested does show unexpected results[2]. Applicant can find no support for the Examiner's contention that unexpected results must be seen at every data point[3]. The principle set forth in *In re Soni* is "that which would have been surprising to a person of ordinary skill in a particular art would not have been obvious." *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995). The data as a whole shows unexpected results for each CpG oligonucleotide and would have been surprising to a person of ordinary skill in the art.

Applicant respectfully reiterates her position that the unexpected results seen with CpG 1758, 1826 and 2006 are representative of the genus of CpG oligonucleotides. In Applicant's Amendment Under 37 C.F.R. § 1.111 filed on July 31, 2003, Applicant previously presented evidence that CpG oligonucleotides are generally expected to act in the same manner since they exert their activity through the Toll-like receptor, TLR9. See Hemmi et al., 2000, Nature 408:740-5 (reference **C01** of record). The Examiner disagrees with the statement in paragraph 6 of the Declaration by Dr. Charlotte Kensil, which states CpGs are expected to act in the same manner with respect to immune adjuvant activity. As support, the Examiner points to Figures 3 and 4 of the present specification as showing that

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[2] The Examiner agrees that Applicant has shown unexpected results with the specific combination of QS-21 and phosphorothioate oligonucleotides 1758 (page 18, lines 12-14, page 23, line 18 to page 24, line 1, and page 25, lines 6-8, of the Office Action mailed August 11, 2004), 1826 (page 20, lines 1-3, and page 21, lines 13-14, of the Office Action mailed August 11, 2004), and 2006 (page 22, lines 8-11 of the Office Action mailed August 11, 2004).

[3] The fact that synergy is shown at all reflects an inherent property of the components themselves, which predictably can be exhibited at concentrations deducible by routine experimentation for each particular subject to which the components are administered.

CpG 1758 and 1826 provide different IgG1 titers and that 1758 caused less antibody production than no adjuvant. Applicant points out that the different IgG1 titers seen in Figures 3 and 4 can be attributed to the differences in the experimental systems. Figure 3 shows the response to a T-dependent antigen (ovalbumin) in C57BL/6 mice after three immunizations. Many T-dependent antigens, such as ovalbumin, will typically have an IgG1 response in the absence of adjuvant because they contain T helper epitopes. Figure 4 shows a T-independent antigen in Balb/c mice and with only two immunizations. Applicant points out that magnitude of response will depend on the experimental system and antigen, and thus will vary, but this variation is not indicative of the fact that there is not a common immune adjuvant activity that is shared among CpG oligonucleotides as a genus.

The examples presented in the present specification and in WO 00/62800 utilized the CpG oligonucleotide at a concentration where little or no adjuvant activity is seen, and it is clear that all three CpG oligonucleotides tested demonstrate a synergistic effect when combined with QS-21. Applicant's previous arguments regarding the mechanism of action of CpG oligonucleotides is not rendered moot simply because at one concentration CpG 1758 did not stimulate an immune response. Thus, the unexpected results are representative of the genus of CpG oligonucleotides.

Applicant respectfully reiterates her position that the unexpected results seen with QS-21 is representative of the genus of QS saponins. Applicant has previously presented remarks showing that immune adjuvant activity is a general property of QS saponins. See Declaration of Dr. Charlotte Kensil, ¶¶ 7-11. The Examiner contends that since QS-21 shows adjuvant activity at some concentrations, but not others, one of ordinary skill in the art could not reasonably conclude that QS-21 would exhibit synergy in any immune activity. Applicant wishes to point out that Figure 2 of the present application does show an immunostimulatory effect for 10 μg QS-21, as acknowledged by the Examiner at page 23, line 12 of the Office Action mailed August 11, 2004. QS-21 does show adjuvant activity, albeit not at low concentrations (which may be due to limits of detection of the assay). This is simply a dose response effect. The fact that, at some concentrations, QS-21 does not show detectable adjuvant activity does not refute the statements presented in the Declaration of Dr. Charlotte Kensil. Thus, as indicated in the Declaration of Dr. Charlotte Kensil, this adjuvant activity is expected to be a general property of QS saponins.

Moreover, Applicant disagrees with the Examiner's analysis of the data. First, in Example 2 and Figure 2, the Examiner transposed the data for 50 μg CpG with that of 1.25

μg QS-21 + 10 μg CpG. 50 μg CpG should equal zero, while 1.25 μg QS-21 + 10 μg CpG should be 61. Second, the Examiner alleges that the Examples 1 and 2 of Friede (WO 00/62800) do not show synergism because (1) 2200 is not significantly greater than 2000 statistically and (2) 250 is not significantly greater than 230, respectively. The Examiner is substituting his unsupported beliefs for that of the inventors of WO 00/62800. In describing Example 1 (Figures 1 and 2) and Example 2 (Figures 3 and 4), Friede *et al.* state that "when both adjuvants are combined, a synergistic effect on those responses is clearly demonstrated." See WO 00/62800, at page 25, lines 6-7. Thirdly, the Examiner contends that the data in Example 2 of Friede cannot be relied upon for post-filing evidence of synergy because CpG 2006 was not adequately described in the specification at the time of filing or in the art at the time of filing. Applicant respectfully disagrees. WO 98/18810 (reference **E07** submitted herewith), published on May 7, 1998, discloses the sequence TCGTCGTTTTGTCGTTTTGTCGTT (SEQ ID NO:56) at page 19, line 18. This sequence corresponds to CpG 2006. Thus, contrary to the Examiner's contention, CpG 2006 was described in the art at the time of filing. Moreover, Applicant emphasizes that it is not necessary for CpG 2006 to have been described in the specification or in the art in order for Applicant to rely on it for post-filing evidence, since it is a member of the genus of CpG oligonucleotides described in the specification.

In view of the foregoing, Applicant respectfully requests that the Examiner withdraw the rejections under 35 U.S.C. § 103.

IV. Double Patenting

Claim 126 has been objected to under 37 C.F.R. § 1.75 as being a substantial duplicate of claim 21. As both of these claims have been canceled, this objection has been rendered moot.

CONCLUSION

Applicant respectfully requests that the amendments and remarks made herein be entered and made of record in the file history of the present application. Withdrawal of the Examiner's rejections and a notice of allowance are earnestly requested. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted,

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Enclosures